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2015

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Braaf, B. (2015). *Angiography and Polarimetry of the Posterior Eye with Functional Optical Coherence Tomography*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Download date: 05. May. 2023

8 Summary

Angiography and polarimetry of the posterior eye with functional optical coherence tomography

Our eyes are incredibly important for our everyday activities and even a partial vision loss due to disease or trauma has an enormous impact on our quality of life. It is therefore important that the tissue structures within the living eye can be visualized to obtain an accurate disease diagnosis and to select the best course of treatment. This thesis focuses on the visualization and functional assessment of the tissue structures at the back of the living human eye (the posterior eye) with specialized ophthalmic microscopes based on optical coherence tomography (OCT). In OCT the echo of reflected laser light is measured with optical interferometry to visualize cross-sectional tissue structures with micrometer resolution. The non-invasive cross-sectional visualization of *in vivo* tissue microstructures with OCT is nowadays an established technique in ophthalmology for clinical assessment of the retina. Besides tissue structures OCT can also measure functional processes, which provide additional relevant information on tissue function. The main aim was to further develop two functional OCT methods for posterior eye imaging: Doppler OCT for the visualization of blood flow (angiography) and polarization-sensitive OCT for optical polarization analysis of fiber structures (polarimetry).

The Doppler effect occurs when light is backscattered by moving particles. Doppler OCT analyzes the phase changes caused by the Doppler effect within successively measured OCT A-scans at the same location. In biological tissue this phenomenon occurs predominantly for erythrocytes and other particles in flow-

ing blood. **Chapter 3** of this thesis describes the construction of an experimental swept-source Doppler OCT instrument at 1040 nm and its calibration against small instabilities in the laser, the interferometer and the data acquisition hardware. For this purpose a new post-processing method was developed in which the OCT interference fringes were resampled to the exact same wavenumber space. This method allowed the removal of fixed-pattern noise artifacts and enabled Doppler OCT measurements of the blood flow in the *in vivo* human retina and choroid. The developed OCT system performed close to the shot-noise limit (<1 dB) while the suppression of fixed-pattern noise artifacts removed all artifacts from the OCT images. The clinical applicability of the system was shown by the Doppler OCT detection of retinal and choroidal blood flow in a healthy volunteer and the detection of tissue reperfusion in a patient after retinal pigment epithelium and choroid transplantation surgery.

In high-speed Doppler OCT systems the evaluation time between successively measured A-scans is short and results in the inability to visualize complete vascular networks since low flow velocities cause insufficient phase changes. In **chapter 4** this problem was solved by comparing B-scans instead of successive A-scans to enlarge the evaluation time interval. A detailed phase-noise analysis of the OCT system was performed in order to calculate the optimal time intervals for angiography of the human retina and choroid. High-resolution images of the vasculature of a healthy volunteer taken with various time intervals confirmed this analysis. Angiographic Doppler OCT imaging was performed with a backstitched B-scan in which pairs of small repeated B-scans were stitched together to independently control the time interval and the imaged lateral field size. An inter-B-scan time interval of ≥2.5 ms was found effective to image the retinal vasculature down to the capillary level. The higher flow velocities of the choroid allowed a time interval of 0.64 ms to reveal its dense vasculature. Clinically, the improved visualization of vasculature with the new Doppler OCT angiography method allowed the detection of a choroidal neovascularization in an age-related macular degeneration patient.

Eye motion can significantly degrade the ability to perform successive OCT measurements at the same location and decreases the Doppler OCT angiography performance. In **chapter 5** inter-B-scan phase-resolved Doppler OCT angiography was combined with real-time eye tracking to solve this problem. A tracking scanning laser ophthalmoscope at 840 nm provided eye tracking functionality and was combined with the experimental swept-source OCT system. Real-time eye tracking corrected eye drift and prevented discontinuity artifacts from (micro)saccadic eye motion in OCT angiograms. This improved the OCT spot stability on the retina and consequently reduced the phase-noise, thereby enabling the detection of slower blood flows by extending the inter-B-scan time interval. In addition, eye tracking enabled the easy compounding of multiple datasets from the fovea

of a healthy volunteer to create high-quality eye motion artifact-free angiograms. High-quality images were obtained from two distinct layers of vasculature in the retina and the dense vasculature of the choroid. Additionally, for the first time, a phase-resolved OCT angiogram of the mesh-like network of the choriocapillaris was obtained containing typical pore openings.

Polarization-sensitive OCT (PS-OCT) determines the optical polarization properties of a sample by depth-resolved polarimetry of the backscattered light. The polarization state of light changes when passing through birefringent structures, which hold a (slightly) different refractive index for different polarization orientations. In tissue fibrous structures like fiber bundles are birefringent, since the refractive index difference between the aligned fibers and their surrounding medium causes an orientation dependent and thus a polarization dependent refractive index. In **chapter 6** an experimental swept-source PS-OCT instrument is described based on single-mode optical fibers with a calibration method against polarization distortions induced by the system hardware components. For this purpose a Jones matrix analysis method was developed that measures and corrects system polarization distortions as a function of wavenumber by spectral analysis of the sample surface polarization state and deeper located birefringent tissue structures. High-resolution B-scan images were measured of the double-pass phase retardation, diattenuation, and relative optic axis orientation to show the benefits of the new analysis method for *in vivo* imaging of the human retina. The correction of system polarization distortions yielded reduced phase retardation noise, and provided better estimates of the diattenuation and the relative optic axis orientation in weakly birefringent tissues. The clinical feasibility of the system was shown by *en face* visualization of the phase retardation and optic axis orientation of the retinal nerve fiber layer in a healthy volunteer and a glaucoma patient. In the latter case a significant reduction in the phase retardation indicated loss of retinal nerve fiber tissue.

It was shown in this thesis that through accurate setup construction and calibration swept-source OCT can be used for non-invasive *in vivo* angiography and polarimetry of the posterior eye. The proper correction of eye motion in real-time and accurate data post-processing provided an imaging quality that is well suited to convincingly visualize pathology in patients. This set the stage for Doppler OCT angiography and PS-OCT polarimetry for their future clinical implementation.